

Derivation of Parkinson's Disease Coded-Stem Cells (PD-SCs)

Grant Award Details

Derivation of Parkinson's Disease Coded-Stem Cells (PD-SCs)

Grant Type: New Cell Lines

Grant Number: RL1-00682

Project Objective: The project objective is to create new cellular models of Parkinson's disease (PD) using iPSC lines derived from both familial PD patients with known mutations (in parkin and PINK1) and sporadic PD patients.

Investigator:

Name:	Zhuohua Zhang
Institution:	Sanford-Burnham Medical Research Institute
Type:	PI

Disease Focus: Parkinson's Disease, Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: \$1,556,448

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Reporting Period: NCE

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Grant Application Details

Application Title: Derivation of Parkinson's Disease Coded-Stem Cells (PD-SCs)

Public Abstract: Parkinson's disease (PD) is currently the most common neurodegenerative movement disorder, severely debilitating approximately 1-2% of the US population. The disease is caused by a selective loss of dopamine-producing neurons located in a specific region of the brain. This loss leads to significant motor function impairment and age-dependent tremors. Unfortunately there is currently no cure for PD, however a synthetic dopamine treatment (L-DOPA), temporarily alleviates symptoms.

The mechanisms of PD progression are currently unknown. However, genetic studies have identified that mutations (changes) in seven genes, including α -synuclein, LRRK2, uclL1, parkin, PINK1, DJ-1 and ATP13A2 cause familial PD. Although the familial form of PD only affects a small portion of PD cases, uncovering the function of these genes may provide insight into the mechanisms that lead to the majority of PD cases.

One of the best strategies to study PD mechanisms is to generate experimental models that mimic the initiation and progression of PD. A number of cellular and animal models have been developed for PD research. However, a model, which closely resembles the human degeneration process of PD, is currently not available because human neurons are unable to continuously propagate (grow) in culture. Human stem cells provide an opportunity to fulfill this task because these cells can grow and be programmed to generate dopamine nerve cells (the neurons under assault in PD patients).

In this study, we propose to create stem cell lines that possess PD-associated mutations in two causative genes, PINK1 and parkin, using either rejected early stage embryos or cultured patient fibroblasts. These cell lines will in effect, represent a model of human PD degeneration of dopaminergic neurons. Our working hypothesis is that PD-associated abnormal parkin or PINK1 genes cause degeneration of stem cell-derived dopaminergic neurons, and dopaminergic neurons in vivo via the same mechanism. We will fulfill three tasks in this study; 1/ To generate the PD-stem cell (PD-SCs) line which harbor abnormal or mutant parkin or PINK1 genes; 2/ To determine the whether the PD-SCs cell lines can form into midbrain dopaminergic nerve cells; 3/ To determine whether mutations in parkin and PINK1 effect the survival of dopaminergic neurons which are derived from the PD-SCs cells. Successful completion of this study will yield novel cellular models for studying the mechanisms involved in PD initiation and progression, and further screening remedies for PD treatment.

Statement of Benefit to California:

Parkinson's disease (PD) is the second leading neurodegenerative disease with no current cure available. Compared to other states, California is the highest in the incidence of this particular disease. First, California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US (Cal Pesticide use reporting system). A commonly used herbicide, paraquat, has been shown to induce parkinsonism in both animals and human. Other pesticides are also proposed as potential causative agents for PD. Studies have shown increased PD-caused mortality in agricultural pesticide-use counties in comparison to those non-use counties in California. Second, California has the largest Hispanic population. Studies suggest that incidence of PD is the highest among Hispanics (Van Den Eeden et al, American Journal of Epidemiology, Vol 157, pages 1015-1022, 2003). Thus, finding effective treatments of PD will significantly benefit citizens in California.

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